CLINICAL PROFILE OF SYSTEMIC LUPUS ERYTHEMATOSUS AMONG CHILDREN LESS THAN 12 YEARS

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M.D DEGREE (PEDIATRICS)
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CERTIFICATE

This is to certify that the dissertation titled **"CLINICAL PROFILE OF SLE IN CHILDREN LESS THAN 12 YEARS"** submitted by Dr.A.SENTHIL KUMAR to the Faculty of pediatrics, The Tamilnadu Dr. M.G.R. Medical university, Chennai in partial fulfillment of the requirement for the award of M.D. Degree (Pediatrics) is a bonafide research work carried out by him under our direct supervision and guidance.

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CONTENTS

RODUCTION

SLE is an episodic multisystem autoimmune disease characterised by widespread inflammation of bloodvessels and connective tissues and by the presence of antinuclear antibodies especially antibodies to native double stranded DNA. Its clinical manifestations are extremely variable and its natural history is unpredictable. Untreated SLE is often progressive and has a significant fatality rate.[1]

It is the second commonest pediatric rheumatic disorder next to juvenile idiopathic arthritis. The clinical course can range from mild to severe and can be potentially life threatening. [1-5]

SLE is a relatively rare disease in childhood with estimated incidence ranging from 10 to 20 per 1lakh children depending on the ethnic population. [1-5]

Hence the study is undertaken to know about the varied clinical presentation, immunological status, disease activity and damage to organs at follow up.

SYSTEMIC LUPUS ERYTHEMATOSUS

Lupus - the latin word for wolf.[1] Kaposi in 1872 described the skin lesions. Osler described the systemic nature of the illness.SLE is an episodic, multisystem, autoimmune disease characterised by widespread inflammation of blood vessels and connective tissues and by the presence of antinuclear antibodies(ANAs).

EPIDEMIOLOGY

Prevalence in asians is three times more than in whites. In afro caribbeans it is six times more common than in whites. 15 to 17% of cases have onset in childhood. Onset is rare before 5 years and uncommon before adolescence. When we take sex ratio girls are more affected than boy but it varies with age of onset.[1]

GENETIC BACKGROUND

The concordance rate is more in monozygous twins. A connective tissue disorder other than SLE occurs in about 1 in 10 families of patients with SLE. There is 20% increased risk for SLE among first degree relatives. The genes associated are major histocompatibility complex class 2 DR2, DR3 in whites, DR2, DR7 in african-americans, DQ

alleles major histocompatility complex class III, C2, C3, C4A, null, C1q, C1r, C1s, mannose binding protein, tumor necrosis factor-alpha, Fc gamma II,and Fc gamma III.[1]

ETIOLOGY

Unknown except for drug induced lupus. A number of factors may act independently or in concert to trigger onset of the disease. Immune dysregulation in the form of hormones like decrease in androgens and increase in estrogens, in males and females. FSH, LH and prolactin are also elevated. Environmental factors like ultraviolet B, increases immunogenicity of DNA and inflammation. Viral infection, elevated titers of antiviral antibodies probably reflect polyclonal B cell activation. Drugs which are definitely associated are isoniazid, phenytoin, alphamethyldopa, chlorpromazine, ethosuximide, hydralazine, procainamide, primidone and trimethadione. Drugs probably associated are penicillin, penicillamine, carbamazepine, sulphonamides, quinidine, captopril, metoprolol,and minocycline. [1]

CRITERIA FOR CLASSIFICATION

The AMERICAN COLLEGE OF RHEUMATOLOGY criteria 1982 modified in 1997. [14-15] Sensitivity - 96% and specificity-100% in childhood lupus. A child is said to have SLE if any 4 or more of the 11 criteria are present serially or simultaneously, during any time of observation.

They are malar rash, discoid rash, photosenstivity, oral ulcers, arthritis, serositis, renal disorder, neurological disorder, hematological disorder, immunologic disorder and antinuclear antibody.

	CRITERION	DEFINITION
1	Malar rash	Fixed erythema, flat or raised, over the malar prominences, tending to spare the nasolabial folds.
2	Discoid rash	Erythematous raised patches with adherent keratotic, scaling, and follicular plugging; atrophic scarring may occur in older lesions.
3	Photosensitivity	Skin rash as a result of unusual reaction to sunlight

	CRITERION	DEFINITION
4	Oral ulcers	Oral/nasopharyngeal ulcers,usually painless
5	Arthritis	Nonerosive arthritis involving 2 or more peripheral joints.
6	Serositis	Pleuritis or pericarditis
7	Renal disorder	Proteinuria of more than 0.5 gm/day or more than 3+ or cellular casts
8	Neurological disorder	Seizures or psychosis in the absence of offending drugs or known metabolic causes.
9	Hematological disorder	Hemolytic anemia with reticulocytosis or leukopenia < 4000/mm^3 on 2 or more occasions or lymphopenia < 1500/mm^3 on 2 or more occasions or thrombocytopenia < 1,00,000/mm^3 on 2 or more occasions
10	Immunological	Positive LE cell preparation or Anti DNA

	CRITERION	DEFINITION
	disorder	antibody or presence of anti Sm antigen or false positive serological test for syphilis positive for at least 6 months and confirmed by TPI/FTA-ABS
11	Antinuclear antibody	An abnormal titre of ANA by antibody immuno fluorescence or equivalent assay at any point in time and in the absence of drugs known to cause lupus.

CLINICAL MANIFESTATIONS

SLE can present as an insidious, chronic illness, an acute, or a rapidly fatal disease. Constitutional symptoms are common at onset and during exacerbations.

CUTANEOUS MANIFESTATIONS: [16]

Classic butterfly rash is seen in $1/3^{rd}$ to $1/2^{nd}$ of cases. This lesion is not pathgnomonic of SLE. It is symmetric, sparing the nasolabial folds,

slightly raised and well demarcated lesion unlike in JDM which is usually less well demarcated and photosensitive. It is usually non scarring.

Discoid rash is rarely seen in children. It is an erythematous, circular, raised patch which heals with scarring.

Other lesions include maculopapular rashes, petechiae and palpable purpura due to vasculitis, periungual erythema, gangrene, nailchanges, alopecia, subacute lupus, bullous lesions, discoid lupus, photosensitivity, urticarial leukocytoclastic vasculitis, etc.

MUCOSAL INVOLVEMENT

Classic lesion is a painless, shallow, ragged ulcer on the hard palate. It is uncommon. Ulceration or perforation of nasal septum, aphthous stomatitis are common.

ARTHRITIS

Arthritis of small joints usually lasts for 24 to 48 hours. Pain is severe than objective findings, non erosive and can be migratory. Myalgia or proximal muscle weakness is usually prominent.

LUPUS NEPHRITIS: [17-19]

Lupus nephritis is a major determinant of long term outcome. Occurs in about 75% of children. Disease is more frequent and of greater severity in children than in adults.

	HISTOLOGY	MANIFESTATION
Class I	Normal	No detectable disease
Class II A II B	Minimal change disease Mesangial glomerulitis	Minimal proteinuria or Hematuria
Class III	Focal and segmental proliferation	Proteinuria or hematuria, usually does not progress to renal failure

	HISTOLOGY	MANIFESTATION
Class IV	Diffuse proliferative glomerulo nephritis	Nephrotic syndrome and renal insufficiency in 60%
Class V	Membranous glomerulo nephritis	Persistent nephrotic syndrome, hypertension in 30%, renal failure in majority
Class VI	Glomerular Sclerosis	Segmental or extreme sclerosis of glomerulus. Fibrous crescents are common

NEUROPSYCHIATRIC MANIFESTATIONS

Neuropsychiatric manifestations rank second only to nephritis. It occurs in 20 to 40% of cases.

Psychiatric manifestations include depression (most common), suicidal tendencies, visual, tactile hallucinations and emotional lability.

Neurological manifestations include headache, seizures, movement disorders like chorea, ataxia, tremor, hemiballismus, cerebrovascular accidents, cranial and peripheral neuropathy, papilledema, visual loss, vertigo, myelopathy, and cognitive impairment.

CARDIAC MANIFESTATIONS

Pericarditis is most commonly seen in 30% of cases, myocarditis in 10 to 15% of cases, accelerated atherosclerosis and myocardial infarction in long standing cases. The classic lesion is Libman-Sacks endocarditis, which is less common and often subclinical.

VASCULAR DISEASE

Vasculitis affects small blood vessels-arterioles and venules. Raynaud's phenomenon, livedo reticularis, thrombosis, erythromelagia, lupus profundus may occur. Lupus crisis is the sudden development of overwhelming, often fatal, systemic disease due to widespread acute vasculitis.

PLEURO PULMONARY DISEASE

Subclinical disease is common in children. Pleuritis, basilar pneumonitis, pneumothorax, atelectasis, pulmonaryhemorrhage, shrinking

lung (diaphragmatic dysfunction), acute lupus pneumonitis, infections, and interstitial lung disease.

HEMATOLOGICAL MANIFESTATIONS

Hemolytic anemia with reticulocytosis or leukopenia $< 4000/mm^3$ on 2 or more occasions or lymphopenia $< 1500/mm^3$ on 2 or more occasions or thrombocytopenia $< 1,00,000/mm^3$ on 2 or more occasions in the absence of offending drugs. Anemia - most common, usually normocytic, normochromic. Coomb's test is positive in 30 to 40%, less than 10% have overt hemolysis.

IMMUNOLOGIC DISORDER [20]

Positive LE cell preparation or Anti DNA antibody or presence of anti Sm antigen or false positive serological test for syphilis positive for at least 6 months and confirmed by TPI or FTA-ABS.

ANTINUCLEAR ANTIBODY

An abnormal titre of ANA by immuno fluorescence or equivalent assay at any point in time and in the absence of drugs known to cause lupus.

ANTIBODIES	PREVALENCE	SIGNIFICANCE
Antinuclear antibodies	98%	Best screening test
Anti ds DNA	70%	SLE specific; titres correlate with disease activity in some.
Anti Sm	25%	SLE specific
Anti RNP	40%	Seen in overlap syndromes.
Anti Ro (SS-A)	30%	Not SLE specific; associated with sicca syndrome, neonatal lupus, subacute cutaneous lupus, decreased risk of nephritis.
Anti La (SS-B)	10%	Decreased risk of nephritis.
Antihistone	70%	Drug induced lupus.
Antiphospholipid	50%	Coagulation disorders.
Antierythrocyte	60%	Measured as direct Coomb's test.
Antiplatelet	30%	Thrombocytopenia.

ANTIBODIES	PREVALENCE	SIGNIFICANCE
Antineuronal	60%	Active CNS lupus.
Antiribosomal P	20%	Correlates with depression or psychosis.

GASTROINTESTINAL DISEASE

Peritonitis, vasculitis, pancreatitis, colitis, malabsorption, esophageal dysfunction, pseudo-obstruction, paralytic ileus, hepatosplenomegaly, perisplenitis, and functional asplenia may occur.

OCULAR DISEASE

Cotton wool spots, subretinal edema/ hemorrhage, CRV occlusion, episcleritis, papilloedema, retinopathy.

SECONDARY SJOGREN'S SYNDROME

Keratoconjunctivitis sicca and xerostomia.

ENDOCRINOPATHIES

Autoimmune thyroid disease - hypo and hyperthyroidism, steroid induced diabetes mellitus, delayed puberty and menstrual abnormalities.

APPROACH TO MANAGEMENT OF SLE[1]

Counselling, education,team approach
Adequate rest, appropriate nutrition
Use of sunscreen
Immunisation,especially antipneumococcal vaccine
Prompt management of infection
Non steroidal anti inflammatory drugs For musculoskeletal signs and symptoms
Anticoagulation If anticardiolipin antibodies are present in high titres, lowdose aspirin is used. Heparin, followed by warfarin if thrombosis has occurred
Hydroxychloroquine For cutaneous disease and as an adjunct to glucocorticoids for systemic disease
Glucocorticoids Oral prednisolone 1-2 mg/kg/day IV methyl prednisolone initially and at monthly intervals for maintenance therapy in severe disease
Immunosuppressives Azathioprine 1-2 mg/kg/day(PO) Cyclophosphamide 1-2 mg/kg/day(PO) or 500-1000 mg/m2/mo IV in severe disease

AIM OF THE STUDY

1. To study the clinical profile of SLE among children less than 12 years attending an urban referral hospital.

2. SLEDAI scoring at onset and follow up at 1 year.

3. SLICC/ACR-DAMAGE INDEX at 1 year

REVIEW OF LITERATURE

1. Surjit singh et al. studied the clinical and immunological profile of children with SLE at the Dept. of Pediatrics, PGIMER, Chandigarh. [6] They studied 16 cases in the age group 4-12 years. Mean age of children at the time of diagnosis was 10 yr. Female to male ratio was 7:1. Fever, rash, arthritis were common presentation. Renal involvement was noted in 56.2%. ANA positivity is seen in all children. 5 had cardiac involvement and 3 had renal involvement. They concluded SLE must be considered in any child with multisystem disease. [6]

2. L.B.Tucker, division of pediatric rheumatology, British Columbia children hospital, vancouver, BC, canada Lupus(2007)16 546-549.In this article classification criteria for SLE are discussed and an approach to making an accurate and timely diagnosis is considered.[7]

3. FR Pluchinotta et al. Dept of pediatrics rheumatology, university of padova Italy Lupus 2007:16;550 conducted this study with pediatric SLE with onset in infancy, prepubertal and postpubertal age.[8] Postpubertal patients show higher frequency of musculoskeletal involvement and leucopenia, strong female preponderance and more specific signs of disease.

Serological status was not significantly different in the three groups. Prevalence of internal organ involvement seems to decrease with age. Prepubertal patients have an intermediate disease severity and no gender predilection. Infantile SLE showed a significantly higher prevalence of cardiovascular and pulmonary involvement, anemia and thrombocytopenia and shorter disease duration at time of diagnosis.

4. Damage did not independently influence mortality in childhood SLE. Simone Appenzeller.Roberto Marini.Rheumatol Int (2005)25:619-624.In this study 61 patients identified. Six were lost to follow up. Mean SLICC/ACR DI Score was 4.9.Death occurred in 12 of 55 patients. Male gender, the presence of infection and nephritis were independent risk factors for death. Damage did not influence survival in this study.[9]

5. Clinical Features and Outcome of Systemic Lupus Erythematosus. Indira Agarwal, T Sathish Kumar, Kala Ranjini, Chellam Kirubakaran et al reported the clinical profile,treatment and outcome of systemic lupus erythematosus in 70 patients between the ages of 4-15 years at Christian medical college Vellore,India. Fever,arthritis and rash were extrarenal manifestations. Anemia was seen in 60% and direct Coombs test was

positive in 58.3%. Antinuclear antibody was positive in all; anti-double stranded DNA antibody and low C3 levels were seen in 77.1% and 80%, respectively. Renal involvement was noted in 77.1% and included proteinuria (53%), hematuria (42.8%), hypertension (18.5%) and elevated serum creatinine (8.6%). Renal histology showed class I nephritis in 3.7%, class II in 44.4%, class III in 4.3%, class IV in 44.4% and class V in 1.8%. On follow up 18.8 months later, 70% patients were in remission, 7.5% had active disease and 7.5% died. The characteristics of childhood lupus erytematosus were similar to those previously reported. The outcome was favourable in most cases.[34]

6. A. N. Chandrasekaran et al studied 330 adult Systemic Lupus Erythematosus (SLE) cases who attended the Rheumatic Care Centre, Government General Hospital,Chennai. 59 children were analysed. There was no case with onset before the age of 5 years. There were 49 females and 10 males (M:F =1:4.9). The initial manifestations were fever (67%), arthritis (61%), skin rash (59%) and lymphadenopathy (27.1%). There was no case of Raynaud's phenomenon. Only 10.1% of patients presented with thrombocytopenic purpura. In the cumulative clinical features, arthritis in 86.6%, fever in 79.8%, skin rash in 69.4%, lymphadenopathy in 61% and hepatosplenomegaly in 39.9% were observed. Renal involvement was seen

in 49.1%, neuropsychiatric manifestations in 27.1%, pleuropulmonary in 22% and cardiac manifestations in 10.2%. Anemia was seen in 50.8%, leukopenia in 18.4%, thrombocytopenia in 11.8%, ANA in 100%, anti-dsDNA in 92.3%, anti-Sm in 34.7%, anti-SSA in 38.5%, anti-SSB in 15.4%, ACL in 30.8%, low C3 in 50% and false positive VDRL in 3.3%. Death occurred in 8 children, 3 due to infection, 2 due to renal causes, I due to cardiac and 2 due to central nervous system involvement. [21]

7. Severe clinical course of systemic lupus erythematosus in the first year of life was done at the university of Padua,Italy.The conclusions drawn were, SLE very rarely occured before the age of 5years. The clinical and laboratory characteristics of iSLE patients followed at the Department of Pediatrics of Padua were analyzed. A total of 13 patients with iSLE,were included . Seven (53.8%) were females and 6 were males (46.2%). The age at disease onset ranged from 6 weeks to 11 months. In comparison with juvenile systemic lupus erythematosus , iSLE showed a higher prevalence of positive family history for autoimmune diseases, systemic symptoms at presentation, internal organs involvement, and shorter time between symptoms onset and diagnosis. Anemia and thrombocytopenia were present in the majority of the patients at diagnosis, whereas leukopenia was rarely observed. The overall prognosis in iSLE was very poor: 5/13 infants died

between 2 and 31 months after the onset, and 5/13 had severe disease course with residual organ damage. SLE can start as early as during the first year of life and is more severe than in the later age groups.[35]

MATERIALS AND METHODS

METHODOLOGY

Study design - Descriptive/prospective observational study

Study place - Rheumatology clinic, nephrology ward, medical wards of ICH & HC

Study period - Nov 2007 to Aug 2009.

Study population - All children diagnosed to have SLE.

Sample size - 50

INCLUSION CRITERIA

All children < 12 years diagnosed to have SLE.

EXCLUSION CRITERIA

Nil

MANOEUVRE

This study was conducted in medical ward, nephrology ward, rheumatology OPD, in ICH&HC. Clinical features, laboratory

investigations, treatment were followed for all the children. SLE disease activity index and SLICC/ACR damage index was done at diagnosis, and followup at 1year.Children were divided into three groups based on the age of onset as less than 2 years, between 2-10 years and 10-12 years. Clinical features, laboratory investigations and treatment were compared between the groups.

STATISTICAL ANALYSIS

The sample size of the study was 50. Frequency of occurrence of clinical, laboratory, and treatment parameters were derived for all the 50 children. SLEDAI and SLICC/ACR damage index scores had their mean values computed. SLEDAI scores were compared between onset and follow up by One way ANOVA, Fischer test and P values derived. Analysis between three groups of disease occurrence was done by Chi square test and p values obtained. p values less than 0.05 is taken as significant.

RESULTS AND ANALYSIS

TABLE-1

	MEAN	**STANDARD DEVIATION**
AGE AT ONSET OF DISEASE	7.94 YEARS	2.92 YEARS
AGE OF PATIENT	9.46 YEARS	2.69 YEARS
DURATION OF ILLNESS AT DIAGNOSIS	11.06 MO	6.48 MO

Age at onset of disease was 7.94 years (S.D 2.92)

Mean age of patients was 9.46 years (S.D2.69).

Duration of illness in patients prior to diagnosis was 11.06 months. (S.D 6.48)

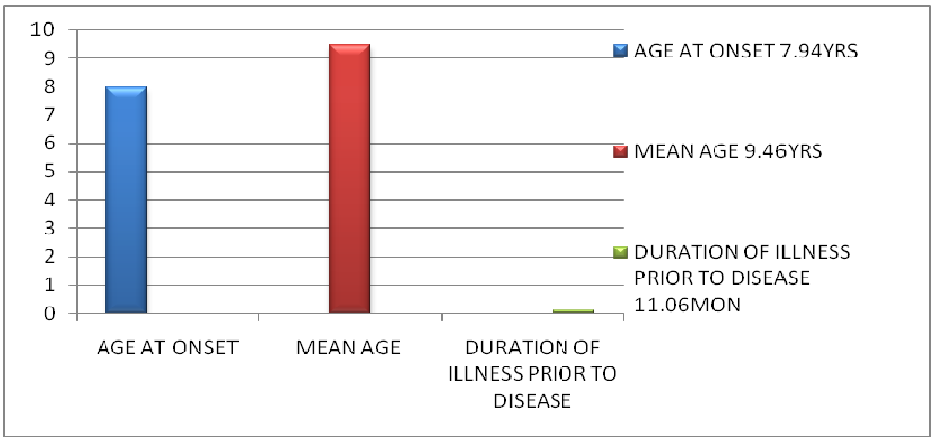
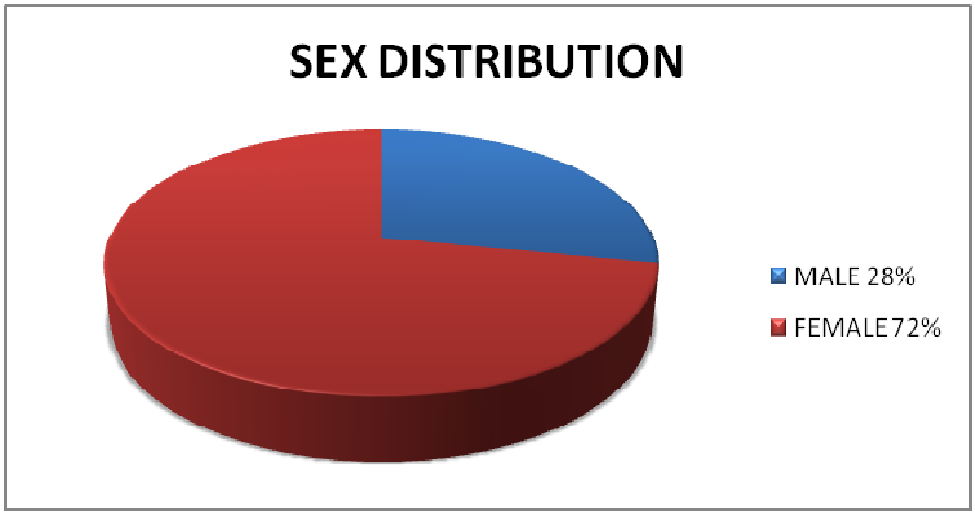


TABLE-2 SEX DISTRIBUTION

SEX	N = 50	%
MALE	14	28
FEMALE	36	72

Female to male ratio was 2.5:1

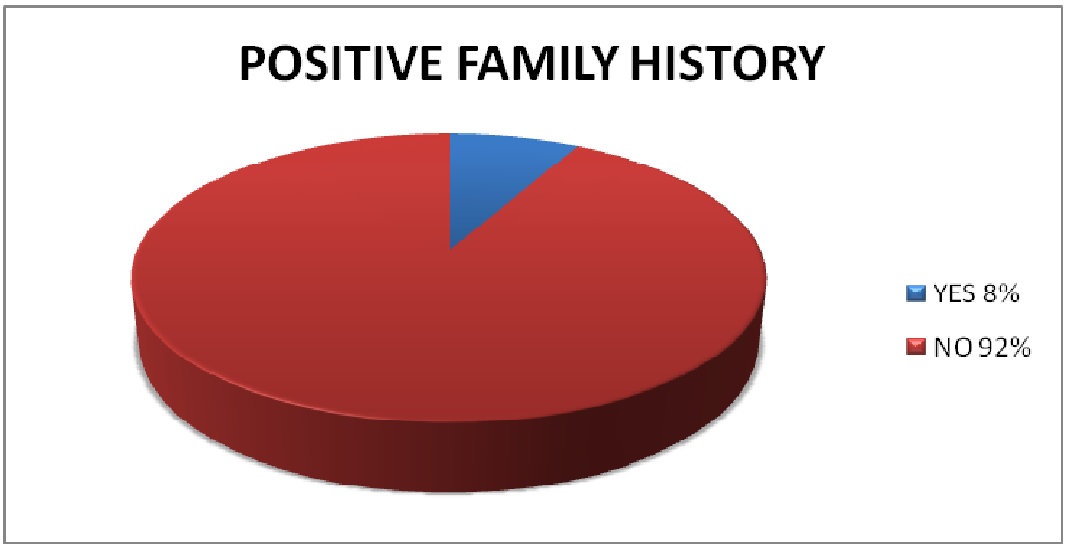


14(28%) of the children were male and 36(72%) of the children were female.

TABLE-3

FAMILY HISTORY

POSITIVE FAMILY HISTORY	N = 50	%
YES	4	8
NO	46	92



Family history of auto immunity in first and second degree relatives is noted in 8% of patients.

TABLE-4

ORGAN INVOLVEMENT-MUCOCUTANEOUS

	N = 50	%
MALAR RASH	36	72
PHOTOSENSITIVITY	26	52
ORAL ULCERS	16	32
ALOPECIA	13	26
DISCOID RASH	2	4
RAYNAUDS	0	0

In mucocutaneous involvement, 36 cases (72%) had malar rash, 26(52%) had photosensitivity and 16 cases (32%) had oral ulcers.

Alopecia was noted in 13 cases(26%) and 2 cases(4%) had discoid rash.

MUCOCUTANEOUS INVOLVEMENT

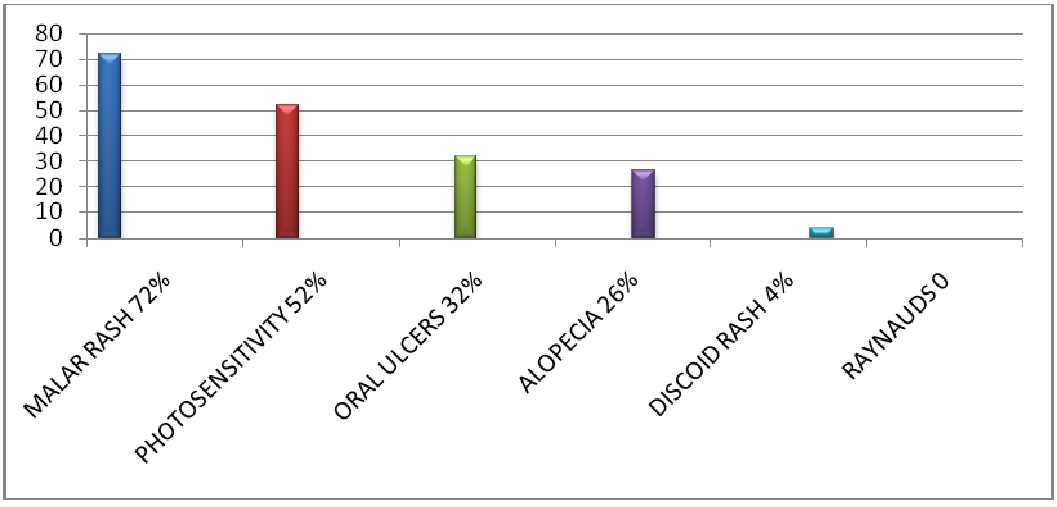


TABLE-5 MUSCULOSKELETAL & RETICULO ENDOTHELIAL SYSTEM INVOLVEMENT

	N = 50	%
ARTHRITIS	30	60
LYMPHADENOPATHY	16	32

In musculoskeletal involvement, arthritis was noted in 30 cases (60%). Reticuloendothelial involvement in the form of lymphadenopathy was found in 16 cases (32%).

MUSCULOSKETAL/RETICULOENDOTHELIAL SYSTEM

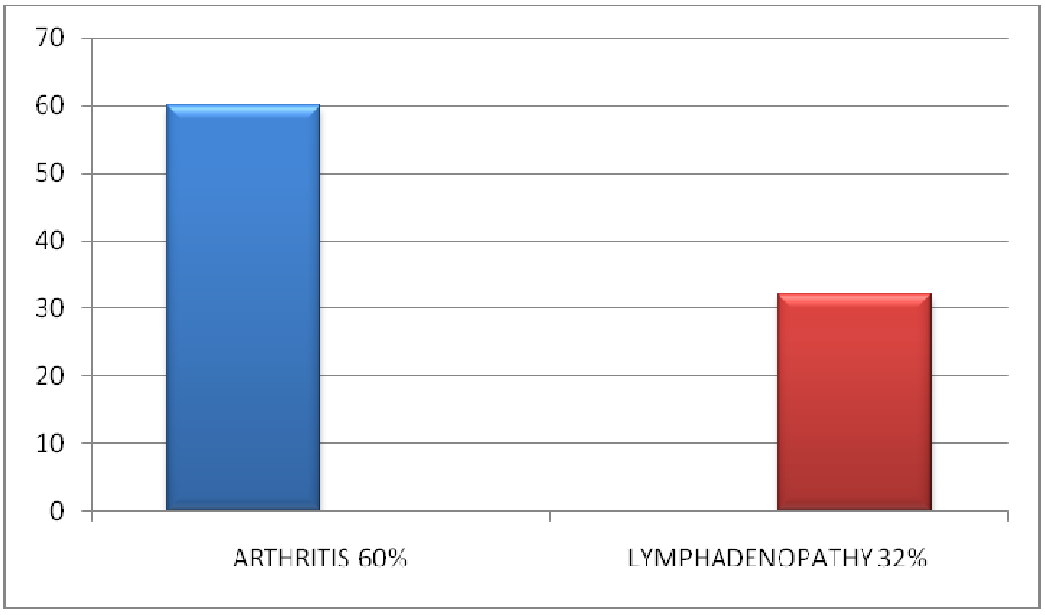


TABLE-6 RENAL INVOLVEMENT

RENAL INVOLVEMENT	N = 50	%
PROTEINURIA >0.5 G/DAY	20	40
NEPHROTIC SYNDROME	15	30
HYPERTENSION	8	16

Proteinuria more than 0.5g/day was found in 20 cases (40%).15 cases (30%) had nephrotic syndrome.8 cases(16%) had hypertension

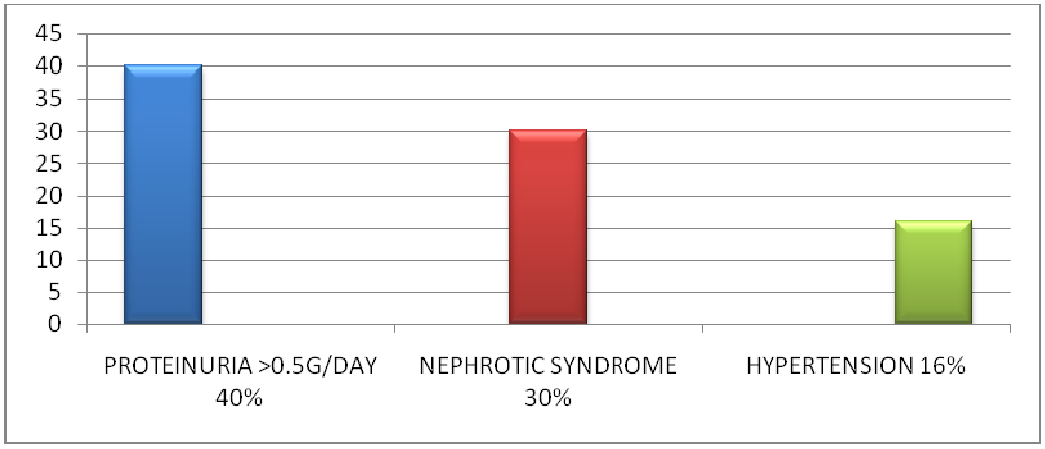


TABLE-7

DISTRIBUTION OF RENAL LESIONS

WHO CLASS	N =14	%	OUTCOME
CLASS 1	1	7.1	IMPROVED
CLASS 2	1	7.1	IMPROVED
CLASS 3	3	21.4	1-DIED
CLASS 4	6	42.8	IMPROVED
CLASS 5	3	21.4	1-DIED

Renal biopsy was done in 14 patients. Class 1 and Class 2 renal lesion was found in 1 patient each (7.1%). Class 3 renal lesion was found in 3 patients (21.4%).Class 4 renal lesion was found in 6 patients(42.8%).Class 5 renal lesion was found in 3 patients(21.4%).

DISTRIBUTION OF RENAL LESIONS

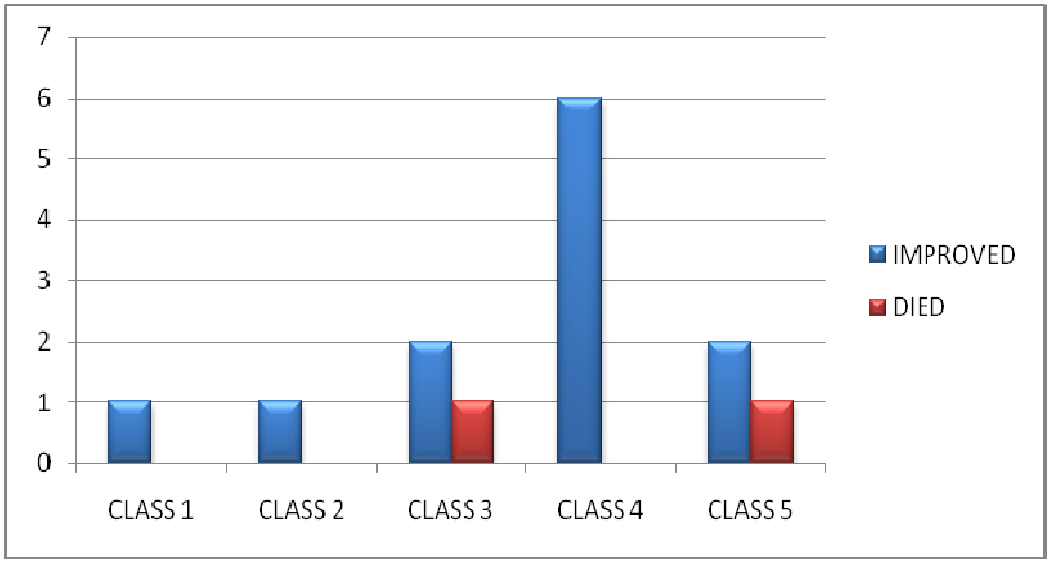


TABLE -8

ORGAN INVOLVEMENT-CVS, RS, GIT, CNS

ORGAN INVOLVEMENT	N =50	%
HEPATOSPLENOMEGALY	35	70
SEROSITIS	19	38
SEIZURES	13	26
CARDIOVASCULAR	4	8

In GIT involvement 35 cases (70%) had hepatosplenomegaly. Serositis was noted in 19 cases(38%). CNS involvement in the form of seizures was noted in 13 cases (26%).Cardiac involvement in the form of valvular lesions was found in 4 patients (8%).

ORGAN INVOLVEMENT

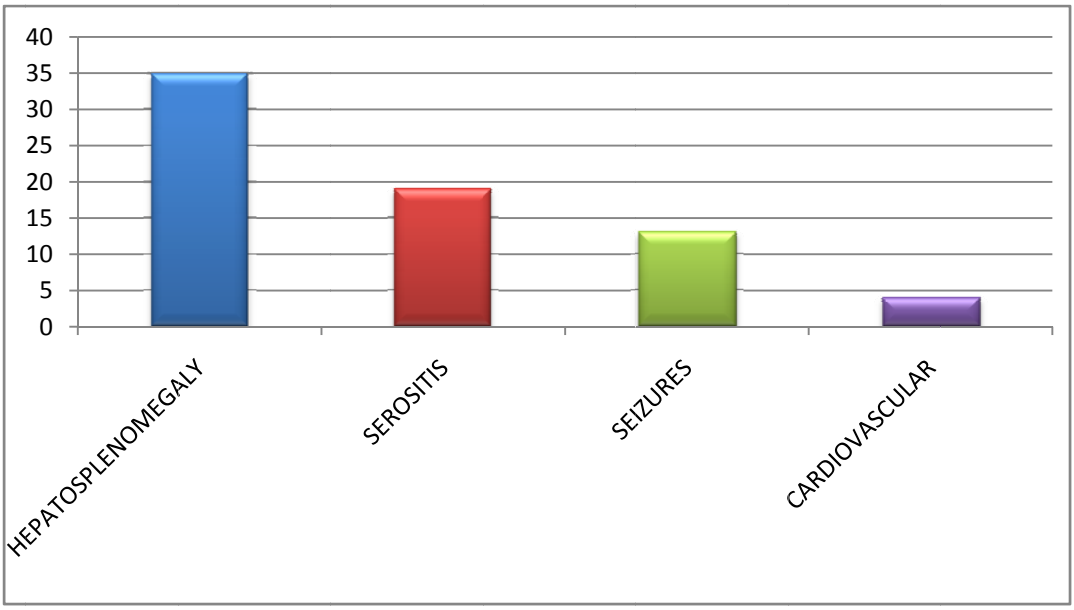


TABLE-9

ORGAN INVOLVEMENT-HEMATOLOGICAL& FEVER

	N = 50	%
FEVER	47	94
HEMOLYTIC ANEMIA	10	20
THROMBOCYTOPENIA	15	30
LEUKOPENIA	3	6

Majority of patients had fever, 47 cases (94%). Hemolytic anemia was found in 10 patients (20%).Thrombocytopenia was found in 15cases (30%). Leukopenia was found in 3 patients (6%).

ORGAN INVOLVEMENT

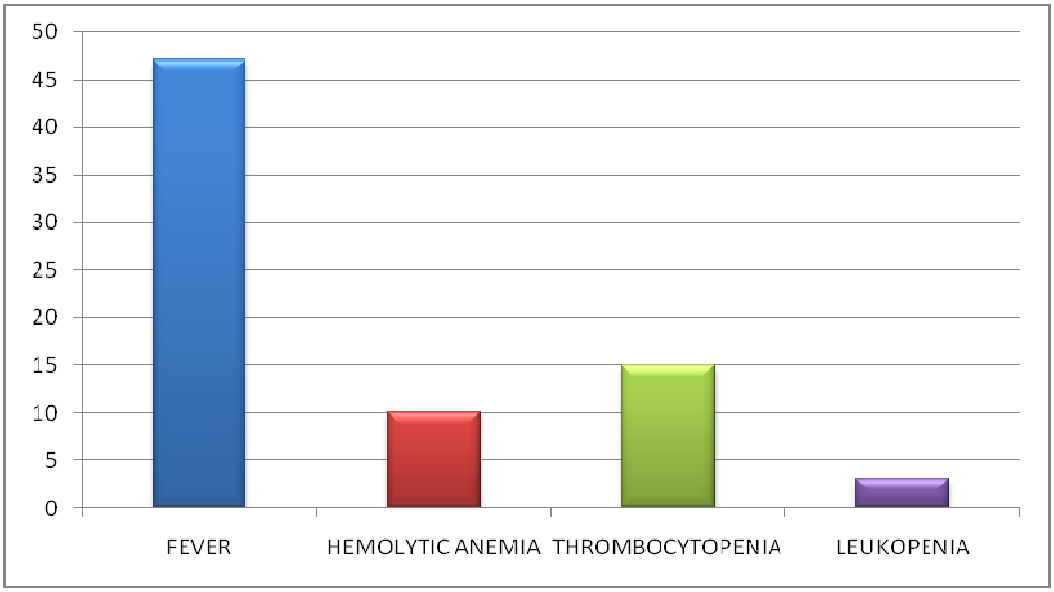


TABLE-10

LABORATORY FINDINGS

LAB FINDINGS	N =50	%
ANA	46	92
ANTI DS DNA	26	52
C3/C4	40	80
ACL/LAC	3(9)	34%

Of the 50 cases with SLE, 46 cases (92%) had ANA positivity. 26cases (52%) had Anti ds DNA positivity.40 cases (80%) had low c3/c4 and ACL/LAC was noted in 3 cases out of 9 cases done(34%).

LABORATORY FINDINGS

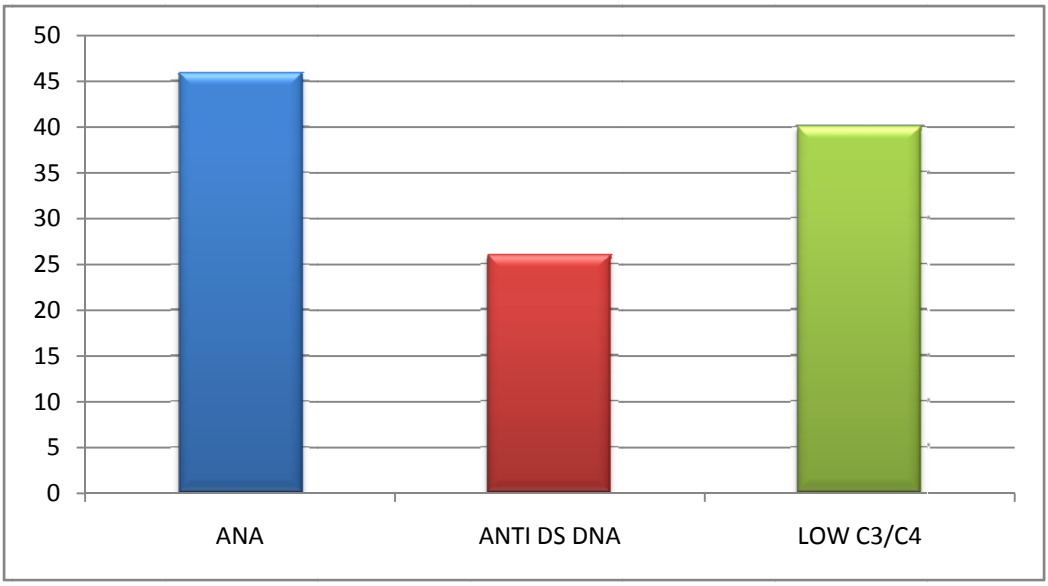


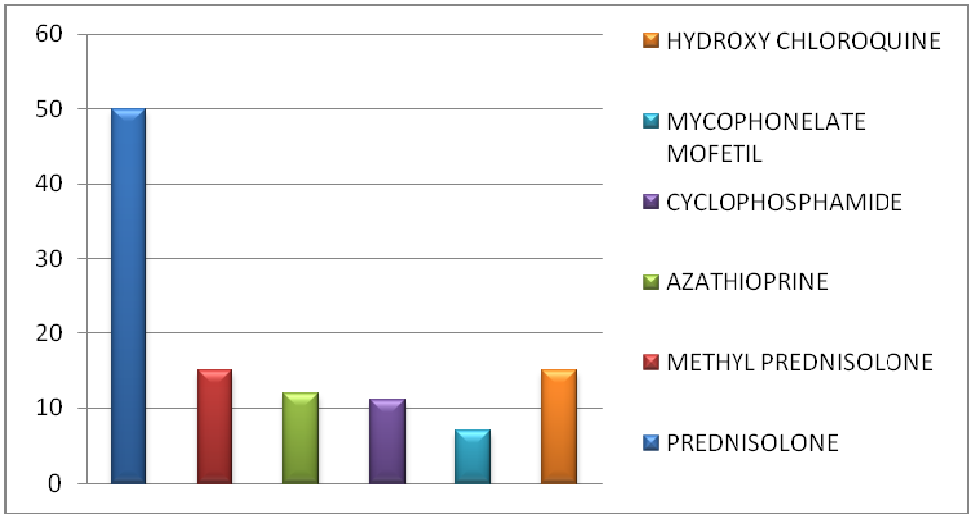
TABLE-11 TREATMENT

TREATMENT	N =50	%
PREDNISOLONE	50	100
METHYL PREDNISOLONE	15	30
AZATHIOPRINE	12	24
CYCLOPHOSPHAMIDE	11	22
MYCOPHONELATE MOFETIL	7	14
HYDROXY CHLOROQUINE	15	30

All the 50 patients (100%) received prednisolone as treatment.15cases (30%) received methyl prednisolone and 12 patients (24%) had azathioprine.

11patients (22%) received cyclophosphamide, 7(14%) had mycophenelate mofetil and 15 cases (30%) had hydroxy chloroquine.

TREATMENT



	INDUCTION		MAINTENANCE		RELAPSE	
	N =50	%	N =50	%	N =50	%
AZATHIOPRINE	4	8	5	10	3	6
CYCLO PHOSPHAMIDE	8	16	0	0	3	6
MMF	5	10	2	4	0	0

Azathioprine was used as induction therapy in 4 cases (8%), maintenance therapy in 5 cases (10%) and in relapse 3 cases (6%).

Cyclophosphamide was used as induction therapy in 8 cases (16%), maintenance therapy in nil (0%), and used in relapse 3 cases (6%).

MMF was used as induction therapy in 5 cases (10%), maintenance therapy in 2 cases (4%) and MMF was not used for any of the relapse.

TREATMENT

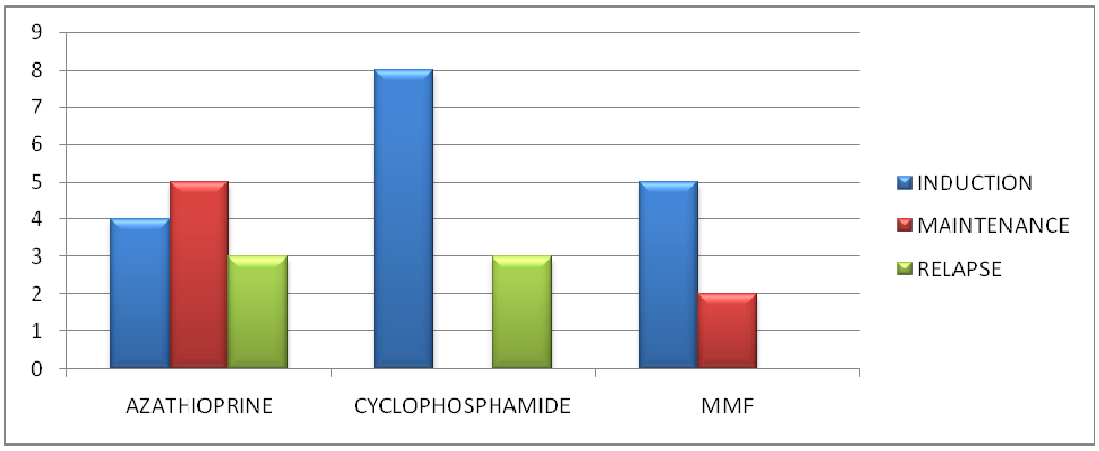


TABLE : 13

SLEDAI SCORE

	MEAN	STANDARD DEVIATION	P VALUE
SLEDAI AT ONSET	12.54	4.94	0.29
SLEDAI AT 1 YEAR	10.02	4.47	0.32

SLEDAI Score at onset had mean of 12.54(S.D 4.94). p value was 0.29. SLEDAI score at followup of one year was 10.02(S.D 4.47). P value was 0.32.

MEAN SLEDAI SCORE

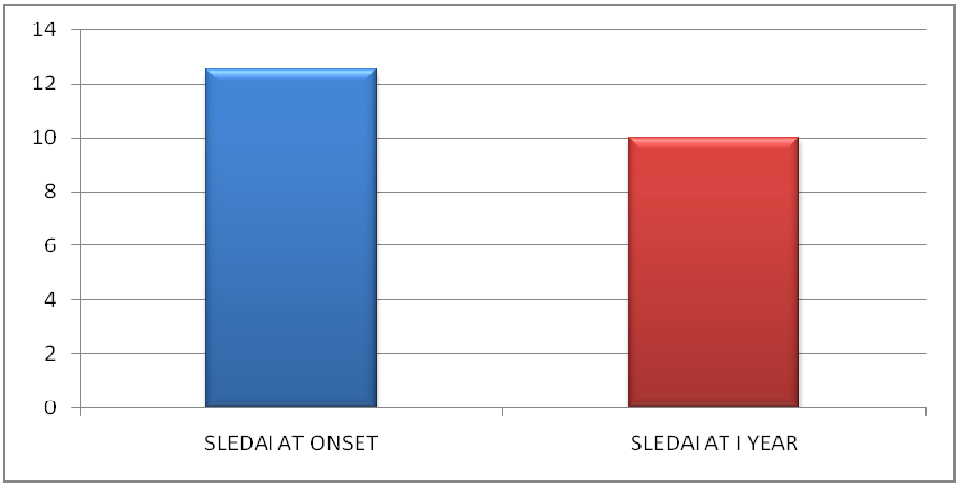


TABLE 14

SLICC/ACR DAMAGE INDEX

	MEAN	STANDARD DEVIATION	P VALUE
SLICC/ACR	0.68	1.63	0.38

SLICC/ACR DAMAGE INDEX at the end of 1 year had mean of 0.68(S.D 1.63). p value was 0.3.

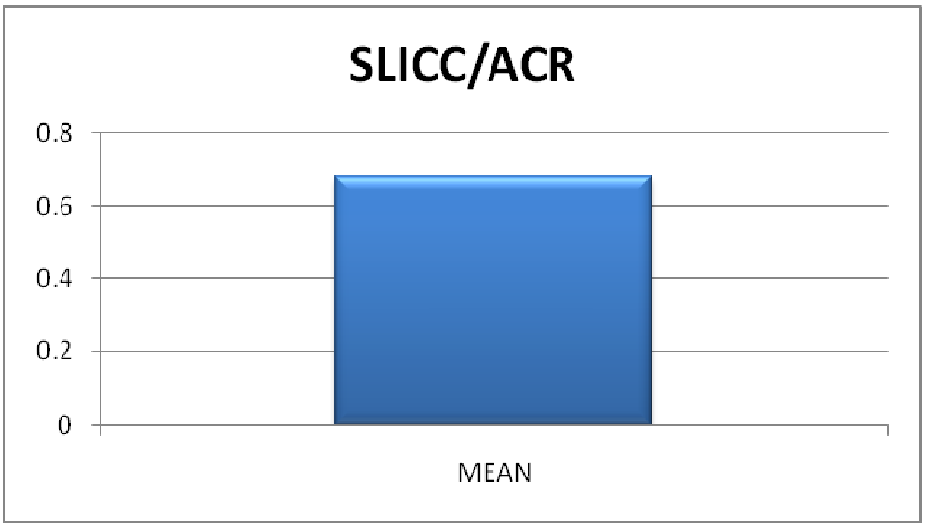


TABLE 15

AGE DISTRIBUTION

AGE	N=50	%
<2	5	10
2-10	26	52
10-12	19	38

Total no of children were 50. Patients were divided into three groups based on age at disease onset. Group A constituted 5 cases (10%), Group B constituted 26 cases (52%), and Group C 19 cases (38%).

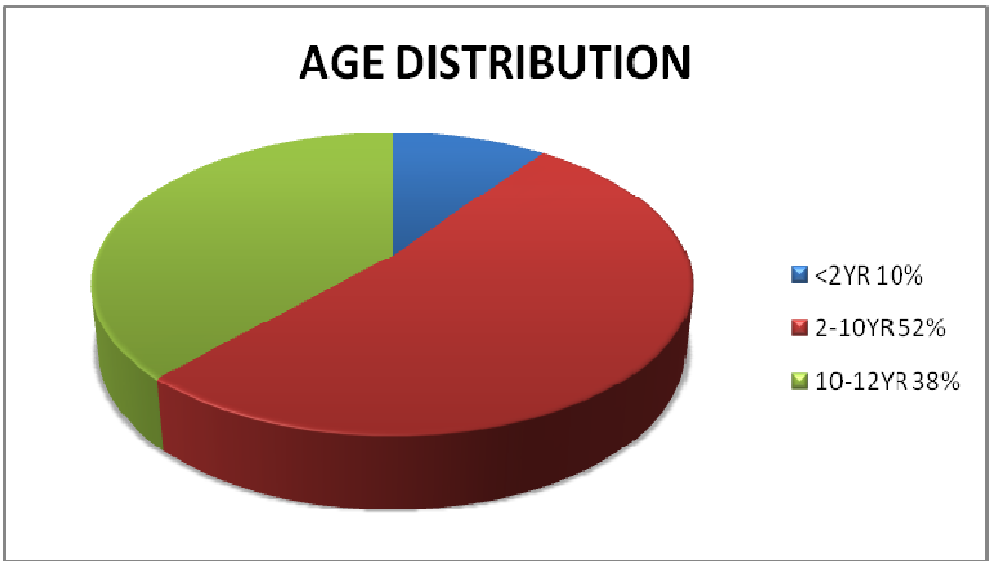

AGE DISTRIBUTION
<2YR 10%
2-10YR 52%
10-12YR 38%

TABLE - 16

SEX DISTRIBUTION

SEX	<2YRS		2 – 10YRS		10 – 12 YRS		TOTAL	
DISTRIBUTION	NO	%	NO	%	NO	%	NO	%
MALE	1	20	6	23.1	7	36.8	14	28
FEMALE	4	80	20	76.9	12	63.2	36	72

14(28%) of the children were male and 36 (72%) of the children were female. Female to male ratio was 2.5:1. Female to male ratio was 4:1 in Group A, 3.3:1 in Group B, and 1.7:1 in Group C.

SEX DISTRIBUTION

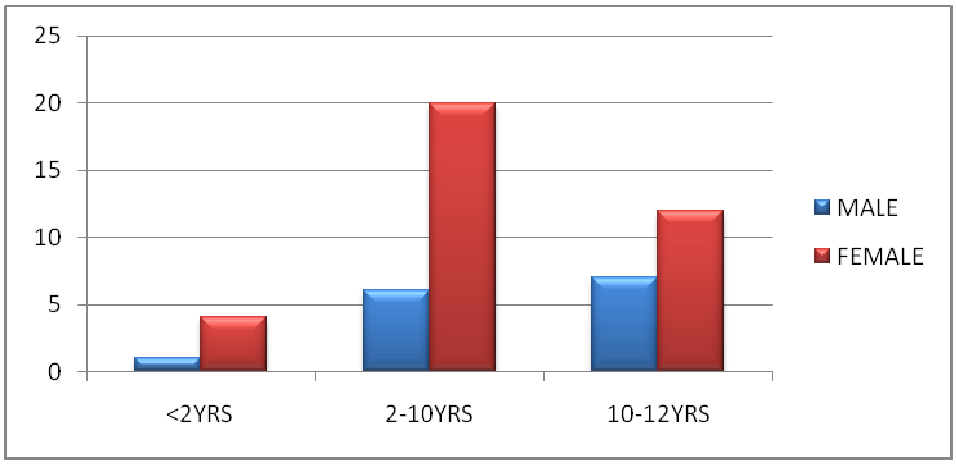


TABLE 17: CHARACTERISTICS OF THREE GROUPS

	GROUP A N =5	GROUP B N =26	GROUP C N = 19	P VALUE
F:M	5:0	3.3:1	1.7:1	NS
MEAN DURATION AT DIAGNOSIS	3.8	9.2	15.15	P<0.01

F: M ratio was 5:0 in Group A, 3.3:1 in Group B, and 1.7:1 in Group C. p value was not significant. Mean duration of illness at diagnosis in months was 3.8 in Group A,9.2 in Group B and15.15 in Group C.

TABLE: 18 ORGAN INVOLVEMENT-MUCOCUTANEOUS

	GROUPA		GROUP B		GROUP C		P VALUE
	N=5	%	N=26	%	N=19	%	
MALAR RASH	4	80	17	65.4	15	78.9	0.55
PHOTOSENTIVITY	2	40	13	50	11	57.9	0.74
ORAL ULCERS	2	40	21	80.8	11	57.9	0.01
ALOPECIA	1	20	8	30.8	4	21.1	0.09

Malar rash was noted in 4 cases (80%) in Group A, 17 cases (65.4%) in Group B and 15 cases (78.9%) in Group C. p value was 0.55.

Photosenstivity was noted in 2 cases (40%) in Group A, 13 cases (50%) in Group B and 11 cases (57.9%) in Group C. p value was 0.74

Oral ulcers was found in 2 cases (40%) in Group A, 21 cases (80.8%) in Group B and 11 cases (57.9%) in Group C. p value was 0.01 which is significant. Alopecia was found in 1 case (20%) in Group A, 8 cases (30.8%) in Group B and 4 cases (21.1%) in group C. p value was 0.09.

MUCOCUTANEOUS INVOLVEMENT IN %

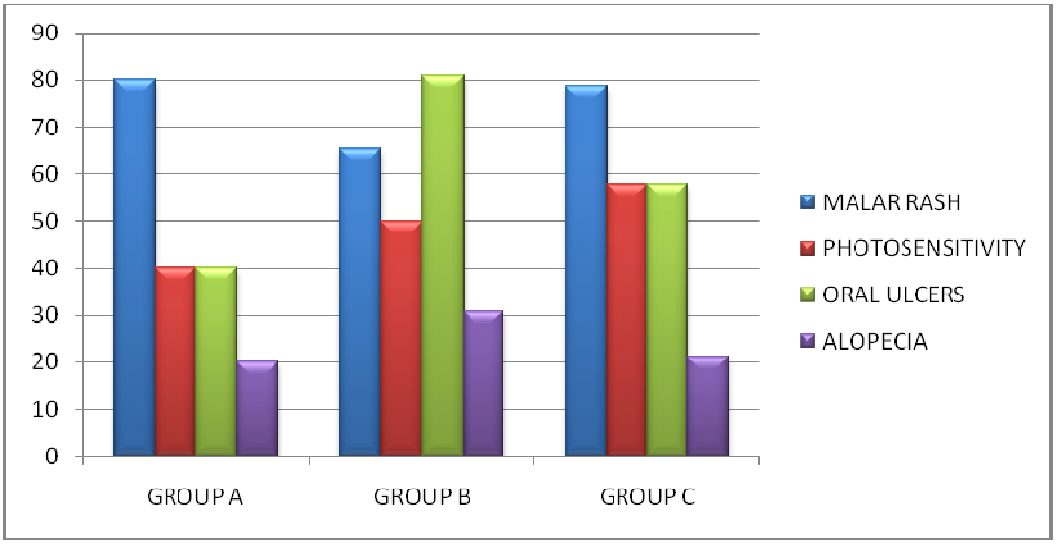


TABLE 19 ORGAN INVOLVEMENT MUSCULOSKELETAL& RETICULOENDOTHELIAL

	GROUP A		GROUP B		GROUP C		P VALUE
	N=5	%	N=26	%	N=19	%	
ARTHRITIS	4	80	15	57.7	11	57.9	0.63
LYMPHADENOPATHY	2	40	10	38.5	4	21.1	0.4

Arthritis was found in 4 cases (80%) in Group A, 15 cases (57.7%) in Group B and 11 cases (57.9%) in Group C.

Lymphadenopathy was noted in 2 cases (40%) in Group A, 10cases (38.5%) in Group B and 4 cases (21.1%) in Group C.

ORGAN INVOLVEMENT IN %

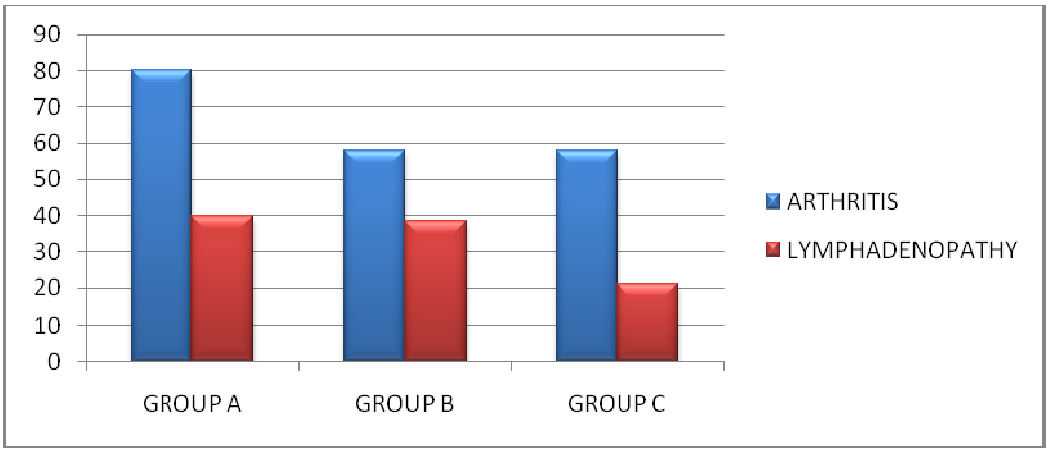


TABLE 20L RENAL INVOLVEMENT

	GROUP A		GROUP B		GROUP C		P VALUE
	N=5	%	N=26	%	N=19	%	
PROTEINURIA	3	60	9	34.61	9	47.36	0.03 S
NEPHROTIC SYNDROME	1	20	7	26.9	6	31.6	0.8
HYPERTENSION	0	0	3	11.5	5	26.3	0.24

Proteinuria was found in 3 cases (60%) in Group A, 9cases (34.61%) in Group B and 9 cases (47.36 %) in Group C. p value was 0.03

Nephrotic syndrome was found in 1 case (20%) in Group A, 7 cases (26.9%) in Group B and 6 cases (31.6%) in Group C. p value was 0.8.

Hypertension was found in 3 cases (11.5%) in Group B and 5 cases (26.3%) in Group C. p value was 0.24.

RENAL INVOLVEMENT IN %

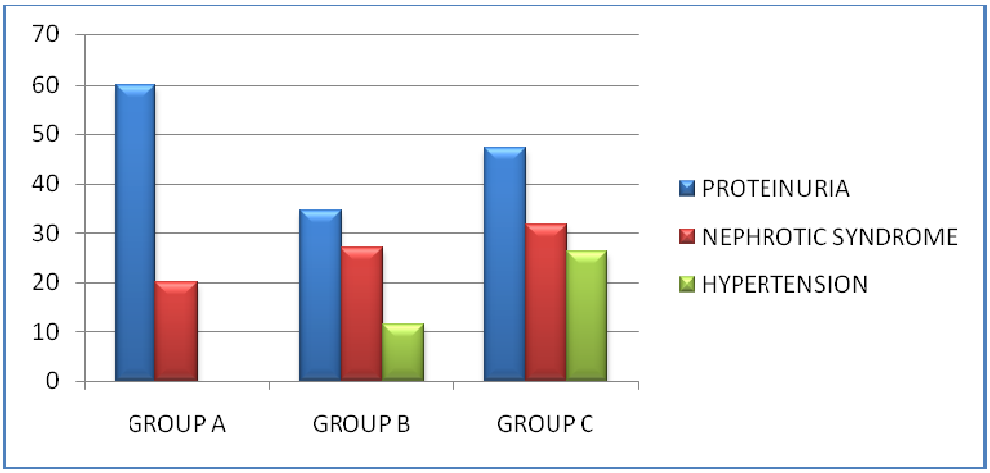


TABLE 21 OTHER SYSTEM INVOLVEMENT

	GROUPA		GROUP B		GROUP C		P VALUE
	N=5	%	N=26	%	N=19	%	
CVS- VALVULAR	1	20	1	3.8	2	10.5	0.13
RS – SEROSITIS	4	80	6	23.1	9	47.36	0.01 S
GIT - HEPATO SPLENOMEGALY	5	100	18	69.2	12	63.2	0.27
CNS – SEIZURES	0	0	8	30.8	5	26.31	0.31
HEMOLYTIC ANEMIA	3	60	4	15.4	2	10.5	0.03 S
LEUKOPENIA	0	0	1	3.8	2	10.5	0.54
THROMBOCYTOPENIA	3	60	6	23.1	6	31.6	0.25
FEVER	5	100	24	92.3	18	94.7	0.8

In SLE, CVS involvement in the form of valvular lesions was found in 1patient (20%) in Group A, 1 patient in Group B (3.8%) and 2 patient (10.5%) in Group C. p value was 0.13.

RS involvement in the form of serositis was found in 4 cases (80%) in Group A, 6 cases (23.1%) in Group B and 9 cases (47.36%) in Group C, p value was 0.01 which is significant.

GIT involvement in the form of hepatosplenomegaly was found in 5 cases (100%) in Group A, 18 cases (69.2%) in Group B, and 12 cases (63.2%) in Group C. p value was 0.27.

CNS involvement in the form of seizures was found only in 8 cases (30.8%) in Group B and 5 cases (26.31%) in Group C. p value was 0.31.

3 cases (60%) in Group A, 4 cases (15.4%) in Group B and 2 cases (10.5%) in Group C had hemolytic anemia. p value was 0.03 which is significant.

Thrombocytopenia was noticed in 3 cases (60%) in Group A, 6 cases (23.1%) in Group B and 6 cases (31.6%) in Group C.

Fever was noticed in all cases (100%) in Group A, 24 (92.3%) cases in Group B and 18 cases (94.7%) in Group C. p value was 0.8

OTHER SYSTEM INVOLVEMENT IN %

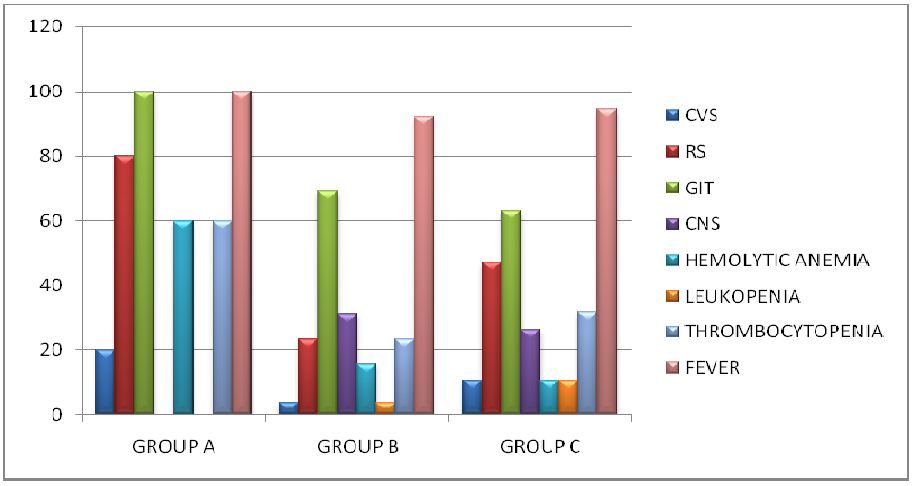


TABLE: 22 LABORATORY FINDINGS

	GROUP A		GROUPB		GROUP C		P VALUE
	N	%	N	%	N	%	
ANA	5	100	24	92.3	17	89.5	0.7
ANTI DS DNA	2	40	14	53.8	10	52.6	0.6
LOW C3/C4	3	60	23	88.5	14	73.7	0.23

ANA positivity was found in all cases (100%) in Group A, 24 cases (92.3%) in Group B and 17 cases (89.5%) in Group C. p value was 0.7

Anti ds DNA positivity was found in 2 cases (40%) in Group A,14 cases (53.8%) in Group B and 10 cases (52.6%) in Group C. p value was 0.6. Low C3/C4 was found in 3 cases (60%) in Group A, 23 cases (88.5%) in Group B and 14 cases (73.7%) in Group C. p value was 0.23.

LABORATORY FINDINGS IN %

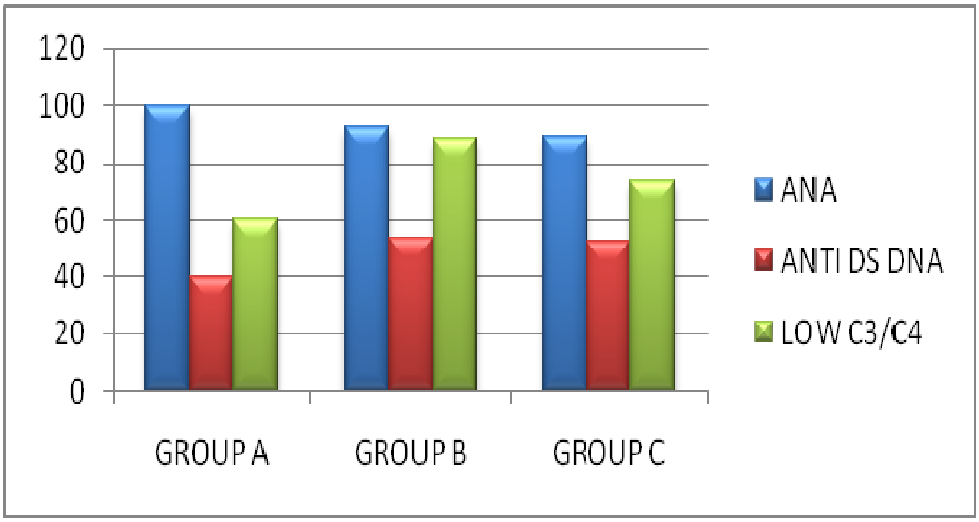


TABLE: 23

TREATMENT

	GROUP A		GROUP B		GROUP C		P VALUE
	N	%	N	%	N	%	
PREDNISOLONE	5	100	26	100	19	100	-
METHYL PREDNISOLONE	0	0	8	30.8	6	31.6	0.84
AZATHIOPRINE	1	20	5	19.2	6	31.6	0.51
CYCLOPHOSPHAMIDE	2	40	4	15.3	5	26.3	0.3
MMF	0	0	3	11.5	4	21	0.14
HYDROXY CHLOROQUINE	1	20	7	26.9	7	36.8	0.62

Prednisolone was used in all cases (100%).Methyl prednisolone was used in 8 cases (30.8%) in Group B and 6cases (31.6%) in Group C.

Azathioprine was used in 1 case (20%) in Group A, 5 cases (19.2%) in Group B, and 6 cases (31.6%) in Group C. p value was 0.51.

Cyclophosphamide was used in 2 cases (40%) in Group A, 4 cases (15.3%) in Group B and 5 cases (26.3%) in Group C. p value was 0.3.

MMF was used in 3 cases (11.5%) in Group B, and 4 cases (21%) in Group C. p value was 0.14.

Hydroxy chloroquine was used in 1 case (20%) in Group A, 7cases (26.9%) in Group B and 7 cases (36.8%) in Group C. p value was 0.62.

TREATMENT IN %

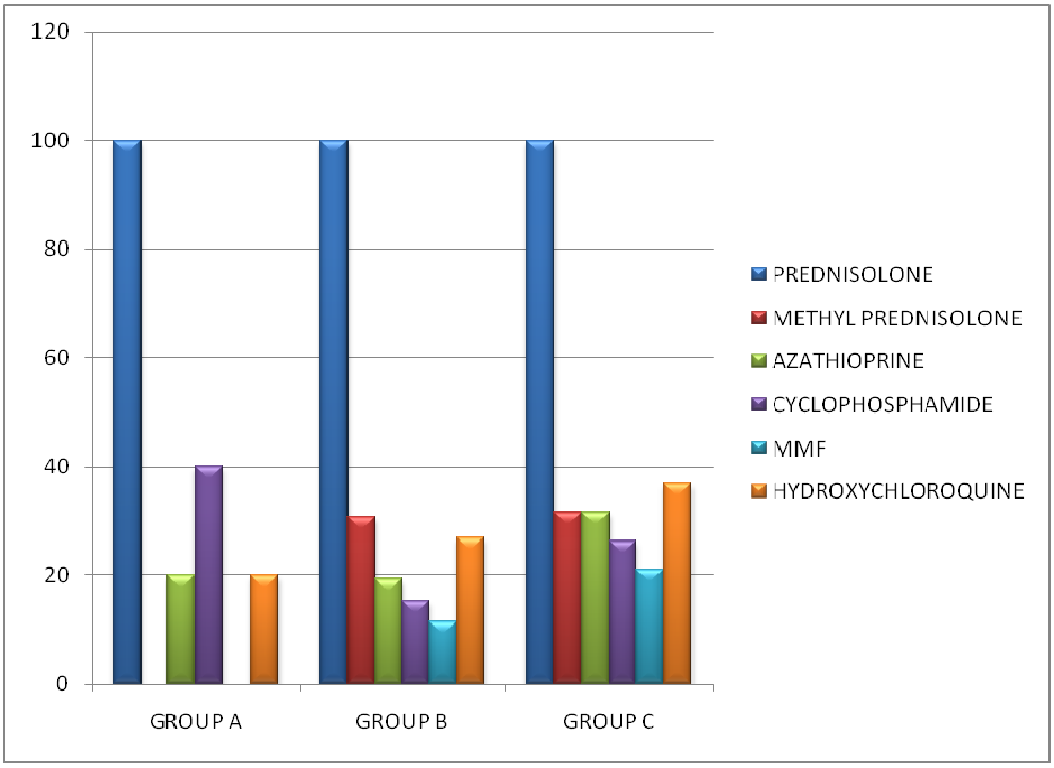


TABLE: 24

	GROUP A		GROUP B		GROUP C		ONEWAY ANOVA
	MEAN	S.D	MEAN	S.D	MEAN	S.D	
SLEDAI AT ONSET	9.6	1.34	13.31	5.69	12.26	4.18	F=1.2 P=0.29

SLEDAI AT 1 YEAR	7.2	1.09	10.5	4.69	10.11	4.58	F=1.16 P=0.32

SLEDAI 1 at onset was 9.6 (S.D 1.34) in Group A, 13.31 (S.D5.69) in Group B and 12.26 (S.D 4.18) in Group C. p value was 0.29.

SLEDAI 2 at 1year was 7.2 (S.D 1.09) in Group A, 10.5 (S.D 4.69) in Group B and 10.11 (S.D 4.58) in Group C. p value was 0.32.

MEAN SLEDAI SCORE

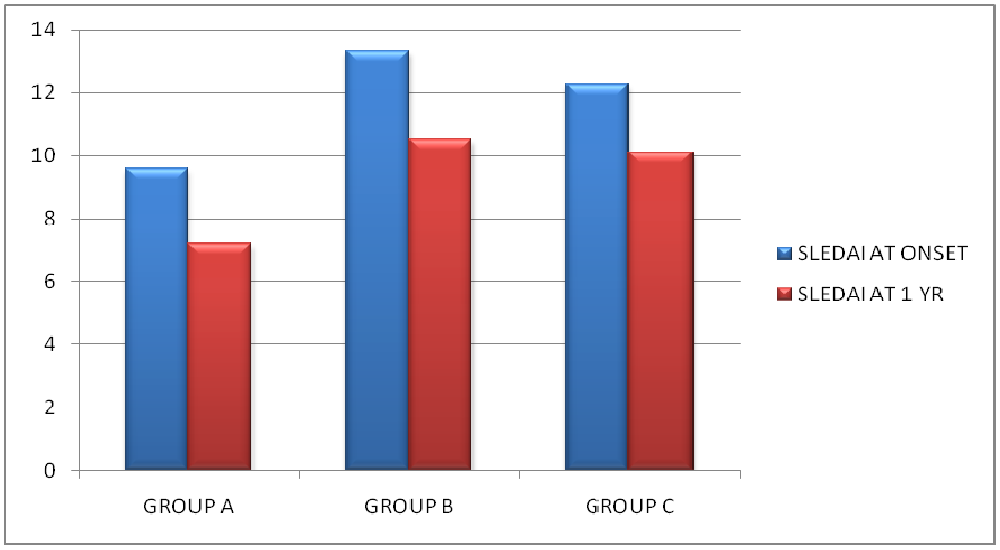


TABLE: 25

	GROUP A		GROUP B		GROUP C		ONEWAY ANOVA
	MEAN	S.D	MEAN	S.D	MEAN	S.D	

SLICC/ACR	0.8	0.83	0.68	1.02	0.61	0.97	P=0.38

SLICC/ACR damage index was 0.8 (S.D0.83) in Group A, 0.68 (S.D 1.02) in Group B and 0.61 (S.D 0.97) in Group C. p value was not significant.

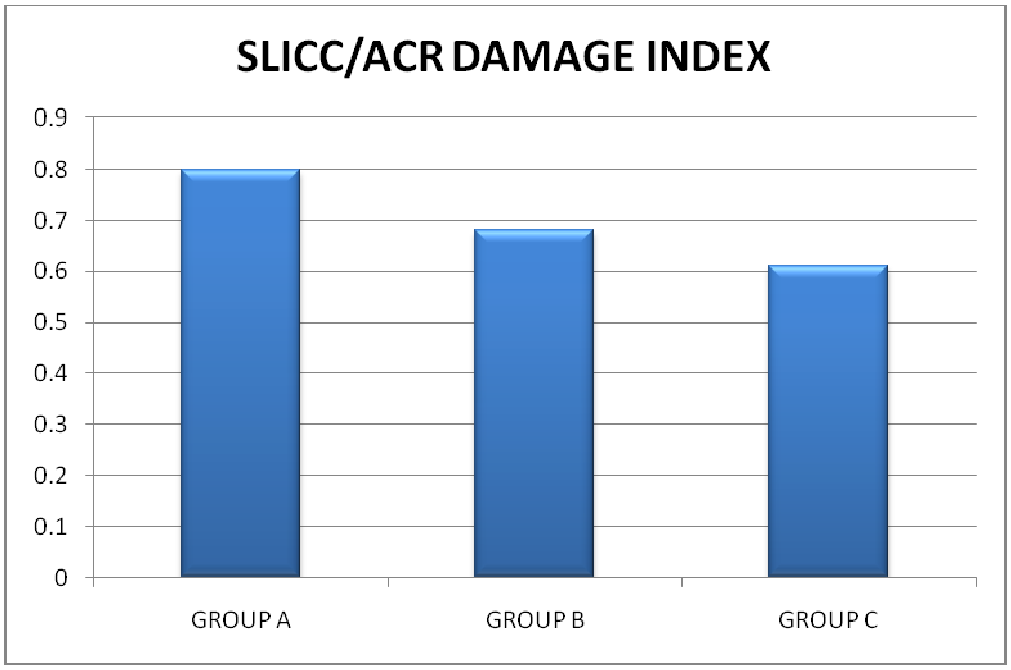


TABLE: 26

DEATH	N	MEAN	S.D	T-TEST

SLEDAI 1	3	22.00	8.8	T=3.88 P=0.01 S
SLEDAI 2	3	15.67	9.86	T=2.36 P=0.01 S

Out of the 3 cases (6%) who died SLEDAI 1 score had a mean of 22 (S.D 8.8). p value was 0.01 which is significant.

SLEDAI 2 at 1 year had a mean of 15.67 (S.D 9.86). p value was 0.01, which is significant.

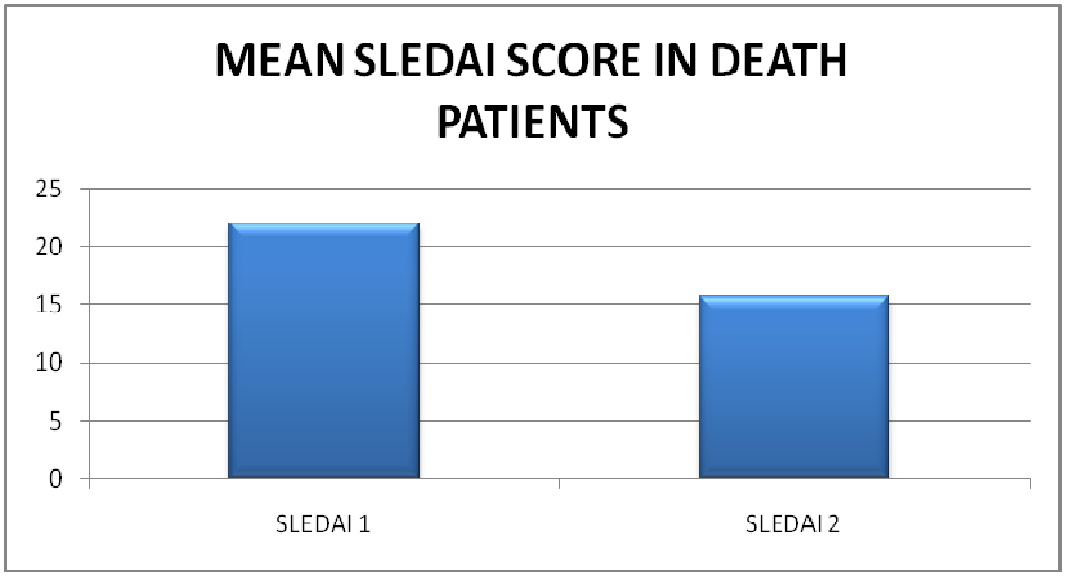
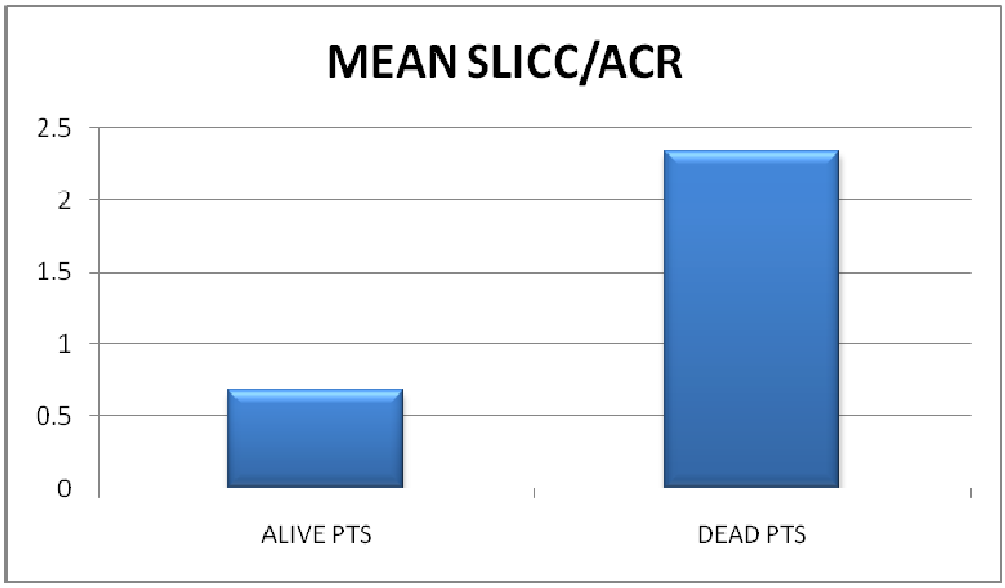


TABLE 27

DEATH	N	MEAN	STANDARD DEVIATION	T-TEST
SLICC/ACR	3	2.33	2.082	T=3.40 P=0.01 S

Out of the 3 cases who died SLICC/ACR damage index had a mean of 2.33 (S.D 2.082). p value was 0.01 which is significant



DISCUSSION

In our study there were 50 cases over the last 2 years. Majority of the children were diagnosed within a year of their initial manifestation. The mean duration of illness prior to diagnosis was 11.06 months in our study. The mean age at the time of onset of symptoms was 7.94 years which is lowest among other pediatric SLE studies from India and abroad [6,21,22]. Female to male ratio in our study is 2.5:1 which is comparable with other studies. Family history of autoimmunity in first and second degree relatives was noted in 8% of patients.

SLE is a multisystem disorder and the manifestations can be variable. In atypical cases the diagnosis may be missed if the suspicion is not high. Such children may continue receiving treatment without diagnosis as exemplified by some cases. Antituberculosis treatment was received by 3 cases before diagnosis. One child being treated as pulmonary tuberculosis and dilated cardiomyopathy and another child with CNS involvement with MRI evidence of demyelination was found to be SLE. Both of them lacked the typical mucocutaneous features.

The most common clinical manifestations were mucocutaneous involvement in the form of malar rash, photosensitivity, oral ulcers, and alopecia. Discoid rash was rare. Raynauds phenomenon was also not noticed. Musculoskeletal involvement in the form of arthritis and reticuloendothelial involvement in the form of lymphadenopathy was also commonly encountered. This is comparable to other series from India [6,21,22] and abroad.[20,23,24,25]

Renal involvement was noticed in the form of proteinuria and nephrotic syndrome. Among the 8 patients with hypertension, 6 of them had renal involvement. Renal biopsy was done in 14 cases out of 20 (70%). Majority of patients with lupus nephritis had pathological changes consistent with class 3, 4, 5 lesion. One patient with class 3 lesion and one patient with class 5 lesion died. 3 patients had peritoneal dialysis and 1 patient was on CAPD.

GIT involvement in the form of hepatosplenomegaly was found in majority of cases (70%). Serositis in the form of pleural or pericardial effusion was noticed in 38% of cases. Cardiovascular manifestations in the form of valvular involvement was found in 4 patients (8%). Dilated cardiomyopathy, pulmonary hypertension, mitral regurgitation and cardiac

tamponade were the manifestations seen. The patient with pulmonary hypertension had anticardiolipin antibody positive which seems to be a manifestation of antiphospholipid antibody syndrome.

CNS involvement in the form of seizures is found in 13 cases (26%). Neuropsychiatric manifestations were found in 2 of these patients. CT scan was done in all of these patients. Cerebral atrophy (2no), CVA with multiple infarct (2no), Intracerebral bleed (2no), demyelination (1no) were the findings. The patient with demyelination had Hodgkins lymphoma. CT scan was normal in rest of the patients.

Fever was noticed in 47 patients. Majority of them presented with pyrexia of unknown origin and later found to be SLE. Hemolytic anemia was found in 10cases. Thrombocytopenia was found in 30% of cases. Leukopenia was found in less no of patients (6%). This is comparable to other studies. [6,20,21,22,23,24,25]. ANA positivity was seen in 46 cases (92%). Anti ds DNA antibody were positive in 52%.Though the value is lower when compared with other pediatric series from India, it is in accordance with international studies [Tan et al]. The reason was most of them were already started on steroids. Hypocomplementemia was noticed in

80%.This is comparable to other studies. ACL/LAC could not be done in all patients. Of the 9 patients done, 3 showed positivity (34%).

Prednisolone was used in all cases. Methyl prednisolone was used in 15 cases (30%) as induction therapy. Azathioprine was used as induction therapy in 8%, maintenance therapy in 10% and 6% cases of relapse. Cyclophosphamide was used in 22% of cases, majority as induction therapy. Children with lupus nephritis received methyl prednisolone and intravenous cyclophosphamide 6 monthly pulse doses to induce remission.

SLEDAI i.e. SLE disease activity index [26] was determined at diagnosis and at follow up after 1 year. SLEDAI 1 had a mean of 12.54 and SLEDAI 2 had a mean of 10.02.This higher score of SLEDAI as compared with other studies suggests higher disease activity, diagnosis at later stages and poor prognosis [27,28]. SLE associated injury was measured by the systemic lupus international collaborating clinics/ACR Damage index. SLICC/ACR-DI [27,28]. It was evaluated at the end of 1 year. It had a mean of 0.68.The lower value as compared with other studies suggest that it should be done frequently and requires follow up on long term basis.

Several studies on pediatric SLE suggest that age at onset modifies the expression of the disease in terms of clinical presentation, pattern of organ

involvement and serological findings[23,30,31,32,33]. In our study we analysed if SLE has different clinical features in three specific age classes. Age less than 2 years constituted 10%, while 2-10years constituted 52% and 10-12 years 38%. Female to male ratio was 5:0 in group A, 3.3:1 and 1.7:1 in group B and group C respectively. Age at onset seems to affect clinical manifestations and prognosis of SLE. Those who had earlier onset had severe disease and worse prognosis. In group A disease duration at diagnosis was significantly shorter than the other 2 groups. In older patients mean disease duration at diagnosis was higher.

No significant difference between the groups was observed in the family history of autoimmune disorders, mucocutaneous involvement, musculoskeletal and reticuloendothelial involvement. Oral ulcers was significantly found in group B. This is in confirmity with other studies exception being musculoskeletal involvement to be rare in infantile SLE and occured with other groups.

Renal involvement was significantly found in infantile

SLE. Nephrotic syndrome had no difference. Hypertension was not found in infantile SLE, but other groups had no difference. Respiratory system involvement occurred significantly in infantile SLE than in other

groups.GIT involvement was found in all infantile SLE patients. CNS involvement was not noticed in infantile SLE, but found in other groups. Hemolytic anemia and thrombocytopenia was significantly found in infantile SLE. Fever had no difference between the groups. Laboratory findings had no difference.

Treatment with prednisolone, azathioprine, cyclophosphamide, MMF and hydroxychloroquine had no difference between the groups. Methyl prednisolone was not used in infantile SLE. Cases with lupus nephritis received methylprednisolone, cyclophosphamide, MMF to induce remission.

SLEDAI as index of disease activity had no difference within the groups. But the score was high. SLICC/ACR Damage index had no difference in the three age classes. Death occurred in 3 cases (6%). Cause of death being infection in all. One died due to sepsis, nocardiosis, lupus nephritis, another due to drug induced hepatitis and third due to infection. SLEDAI score in died patients had significant difference. SLICC/ACR DI had significant values with mean of 2.33.

CLINICAL PRESENTING FEATURES OF CHILDHOOD ONSET SLE (NUMBER AND %)

Characters	ICH present study	Hiraki et al	Rood et al	Font et al	King et al	Casidy et al
No of patients	50	241	31	34	108	58
Malar rash	72	68	52	44	NR	51
Arthritis	60	61	74	65	79	72
Fatigue	_	59	74	NR	33	NR
Renal disease	40	51	45	20	61	84
Fever	94	46	68	41	71	NR
Weight loss	_	34	58	NR	38	NR
Ulcers	32	29	26	9	NR	12
Alopecia	26	27	7	NR	NR	16
Serositis	38	15	32/10	12	NR	31/40
CNS	26	15	10-23	0	13	9
Headache	_	-	36	-	13	-
Photosensitivity	52	15	16	23	NR	16
Raynauds phenomenon	0	15	16	12	NR	16

Characters	ICH present study	Hiraki et al	Rood et al	Font et al	King et al	Casidy et al
Lymphadenopathy	32	14	29	6	39	NR
Hepatosplenomegaly	70	NR	42	NR	28	43

Feature	Present (n=50)	Surgit singh et al(n=16)	Chandrasekaran et al(n=59)	Ali et al (n=20)
Mean age	9.46	8.37	-	9.37
Children<5 years	10	2(12.5%)	0	1(5%)
Female:male	2.5:1	7.1	4.9:1	23:1
Diagnosis at 1 yr	68	66.6	-	-
Nephrotic syndrome	30	31.25	16.9	25
Fever	94	56	67	16
Rash	72	50	59	5
Arthritis	60	50	61	60
Photosensitivity	52	43.7	10.1	5
Hemolysis	20	31	0	-

Feature	Present (n=50)	Surgit singh et al(n=16)	Chandrasekaran et al(n=59)	Ali et al (n=20)
Neuropsychiatric	26	31.25	0	5
Lymphadenopathy	32	18.7	27.1	-
Oral ulcers	32	25	13.5	-
Cardiac	8	18.7	1.6	-
Thrombocytopenia	30	18.7	-	-
Pleuropulmonary	38	12.5	-	-
Raynauds	0	12.5	0	-
Alopecia	26	12.5	11.8	-

SUMMARY

1. SLE can present with protean clinical manifestations.

2. Diagnosis can be missed if the index of suspicion is not high particularly where the typical mucocutaneous features are absent.

3. Even if the classical criteria are not fulfilled some patients on followup turned to be SLE.

4. 1997 ACR classification criteria are appropriate for use in children.

5. Slight female preponderance was found in all age groups.

6. Infantile SLE had onset of disease quite earlier, early renal involvement, respiratory involvement and hematological involvement.

7. Renal involvement in SLE had biopsy of the higher classes (C3, C4, C5) and prognosis is poor. Biopsy was done in 70%. Lupus nephritis children required induction therapy with methylprednisolone, pulse doses of cyclophosphamide, and mycophenolate mofetil. Hence it is suggested that all SLE children should undergo renal biopsy earlier.

8. SLEDAI scoring was high in our children implying disease activity to be severe and diagnosis at later stages.

9. SLICC/ACR DI was low when compared to other studies the reason being one year of followup and the possibility that these children may develop more organ involvement in future.

10. ACL/LAC was not done in all cases suggesting that these parameters can be taken up separately for future studies.

11. The mortality rate was 6%.The cause of death being infection in all the cases. Both the SLEDAI and SLICC/ACR DI were higher.

12. Followup of patients can be continued in further prospective studies in pediatric SLE.

13. Adolescent group can also be taken and compared.

CONCLUSION

SLE could present with varied clinical manifestations,some could be atypical and hence this diagnosis should be considered in case of multisystem involvement. Efforts should be directed in diagnosing at earlier stage itself for better outcome. SLEDAI and SLICC/ACR DI can be incorporated in routine followup to detect mild to moderate and severe flare and extent of organ damage. Renal biopsy can be done in all patients to detect earlier silent involvement, of kidney. Lupus nephritis requires usage of methylprednisolone, pulse doses of cyclophosphamide at monthly intervals and mycophenolate mofetil. Adolescent group can be taken for future prospective studies.

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